Inclusion *Excalibur* 1 and 2

Included patients must fulfil the following criteria

1. Primary histology:
    a. Verified adenocarcinoma in colon/rectum, radically resected with adequate margins/pre-operative treatment
2. Liver metastases:
    a. Six or more liver metastases that have progression (or insufficient response on 1st line chemotherapy, including toxicity). and are hence planned for 2nd line chemotherapy
3. If a history of confirmed extra hepatic metastatic lesion or local relapse, this must have been successfully treated more than 2 years ago without a new relapse.

4. Chemotherapy
    a. Planned for 2nd line chemotherapy.
    b. If patients are switched to 2nd line chemotherapy, randomization can only be allowed prior to first evaluation on 2nd line chemotherapy regimen.

5. The patient
    a. Good performance status, ECOG 0 or 1.
    b. Satisfactory blood tests: Hb >10g/dl, neutrophiles >1.0 (after any G-CSF), TRC >75, Bilirubin<1.5 x upper normal level, ASAT, ALAT<5 x upper normal level, Creatinine <1.25 x upper normal level. Albumin above lower normal level.
    c. Women of childbearing potential (WOCBP) must have a confirmed menstrual cycle and a negative highly sensitive pregnancy test prior to inclusion, or two negative pregnancy tests two weeks apart
    d. WOCBP must agree to use a highly effective method of contraception (see section 6.1.2) for the entire period of exposure to the IMP in the trial, plus for one menstrual cycle/30 days after the last exposure due to the genotoxic potential of the IMP
    e. Men that may have sexual relations with a WOCBP during the trial must agree to use a condom during intercourse for the entire period of exposure plus for one sperm cycle / 90 days after the last exposure due to the genotoxic potential of the IMP

6. Signed informed consent and expected cooperation of the patients for treatment and follow up must be obtained and documented according to GCP, and national/local regulations.

Exclusion Criteria Excalibur 1 and 2

Any of the following criteria will exclude participation in the trial:

1. Arterial anatomy not suited for HAI pump-line insertion.
2. Liver metastatic ingrowth to the diaphragm determined by CT-scan and/or MRI/or ultrasound
3. Previous bone or CNS metastatic disease.

4. Non-curable pulmonary or peritoneal metastases, non-regional lymph-nodes, or local recurrence on PET/CT scan, and on CT or MRI thorax/abdomen/pelvis dated within 6 weeks prior to the trial hospital MDT meeting.
5. Patients with known intolerance or allergy to any ingredient of the IMP to be used as standard therapy for that patient must be excluded
6. Breastfeeding women must be excluded
7. Patients with a psychiatric condition that makes participation in the trial impossible or unethical
8. Patients in a poor nutritional state, those with depressed bone marrow function or those with potentially serious infections must be excluded.
9. Any other reason why, in the opinion of the investigators, the patient should not participate.

Exclusion Excalibur 1

1. Any of the following will preclude inclusion into Excalibur 1 (but not into Excalibur 2)
2. BRAF positivity
3. Any sign of extra-hepatic metastatic disease or local recurrence on PET/CT scan, and on CT or MRI thorax/abdomen/pelvis dated within 6 weeks prior to the trial hospital MDT meeting (exception allowed for $\leq$3 resectable lung lesions all $\leq$ 15mm).
4. Liver lesion >10cm
5. Patient BMI > 30
6. Any previous non colorectal malignancy within latest five years
7. Age $\geq$ 70 years